REMARKS

The Invention

The present claims are directed to methods and compositions that make use of the antibiotic, rifalazil, for treating a subject having an infection of *Clostridium (C.) difficile.*

The Office Action

Claims 1-75 are pending. Claims 1-11 and 54-58 are rejected under 35 U.S.C. § 103(a) for obviousness over Chamberland et al. (U.S. Patent No. 6,114,310; hereafter "Chamberland") in combination with Rose et al. (U.S. Patent No. 6,316,433; hereafter "Rose"). Claims 13, 34, 35, 37-53, 59, and 73-75 are rejected under 35 U.S.C. § 103(a) for obviousness over Chamberland in combination with Rose and further in combination with Bostwick et al. (U.S. Patent No. 5,773,000; hereafter "Bostwick"). And claims 12, 14-33, 36, and 60-72 are rejected under 35 U.S.C. § 103(a) for obviousness over Chamberland in combination with Rose and further in view of statements made in Applicant's specification. Each of these rejections is addressed in detail below.

Rejection of Claims 1-11 and 54-58 under 35 U.S.C. § 103(a)

Claims 1-11 and 54-58 stand rejected for obviousness over Chamberland in view of Rose. Applicant respectfully traverses this rejection.

As indicated above, Applicant's claims are directed to methods of treating *C.*

difficile – an organism considered to be difficult to eradicate – with the antibiotic, rifalazil. This invention is reflected in independent claim 1 and dependent claims 2-11, which cover these methods, as well as independent claim 54 and dependent claims 55-58, which feature compositions that include rifalazil in an amount effective to treat a *C. difficile* infection and instructions for administering the rifalazil to the subject.

The present rejection of claims 1-11 and 54-58 stands on the assertion by the Office that it would have been obvious to combine Chamberland's purported teaching that a rifamycin can be used to treat *C. difficile* with Rose's disclosure that rifalazil is a rifamycin that is known to treat bacterial infections. Applicant traverses this rejection because Chamberland does not support the Office's assertion of its teaching.

According to the Office, "Chamberland teaches that rifamycins can be used to treat *Clostridium Difficile* (Claims 15, 16, and 25)." Applicant disagrees. Chamberland's disclosure does not focus on rifamycins, nor does it focus on methods for treating *C. difficile*. Rather, Chamberland discusses compounds referred to as efflux pump inhibitors and their use for preventing the export of substrate molecules from cells. Chamberland generally discusses treatment of microbial infections, but by methods that involve the use of efflux pump inhibitors to reduce export of co-administered antimicrobial agents or inhibit microbial iron availability by reducing export of siderophores (see column 4, lines 7-20).

Nowhere does Chamberland state that rifamycins can or should be used to treat *C. difficile*, as asserted by the Office. Rather, Chamberland mentions *C. difficile* in only one

context, and it is in a list of *89 different bacteria* "to be inhibited through the use of an efflux pump inhibitor." This list, which stretches for example from column 13, line 56 to column 14, line 34, is reproduced below:

> *Pseudomonas aeruginosa, Pseudomonas fluorescens, Pseudomonas acidovorans, Pseudomonas alcaligenes, Pseudomonas putida, Stenotrophomonas maltophilia, Burkholderia cepacia, Aeromonas hydrophilia, Escherichia coli, Citrobacter freundii, Salmonella typhimurium, Salmonella typhi, Salmonella paratyphi, Salmonella enteritidis, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Enterobacter cloacae, Enterobacter aerogenes, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, Francisella tularensis, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia alcalifaciens, Providencia rettgeri, Providencia stuartii, Acinetobacter calcoaceticus, Acinetobacter haemolyticus, Yersinia enterocolitica, Yersinia pestis, Yersinia pseudotuberculosis, Yersinia intermedia, Bordetella pertussis, Bordetella parapertussis, Bordetella bronchiseptica, Haemophilus influenzae, Haemophilus parainfluenzae, Haemophilus haemolyticus, Haemophilus parahaemolyticus, Haemophilus ducreyi, Pasteurella multocida, Pasteurella haemolytica, Branhamella catarrhalis, Helicobacter pylori, Campylobacter fetus, Campylobacter jejuni, Campylobacter coli, Borrelia burgdorferi, Vibrio cholerae, Vibrio parahaemolyticus, Legionella pneumophila, Listeria monocytogenes, Neisseria gonorrhoeae, Neisseria meningitidis,* Kingella, Moraxella, *Gardnerella vaginalis, Bacteroides fragilis, Bacteroides distasonis,* Bacteroides 3452A homology group, *Bacteroides vulgatus, Bacteroides ovalus, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides eggerthii, Bacteroides splanchnicus, Clostridium difficile, Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium intracellulare, Mycobacterium leprae, Corynebacterium diphtheriae, Corynebacterium ulcerans, Streptococcus pneumoniae, Streptococcus agalactiae, Streptococcus pyogenes, Enterococcus faecalis, Enterococcus faecium, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus intermedius, Staphylococcus hyicus* subsp. hyicus, *Staphylococcus haemolyticus, Staphylococcus hominis, Staphylococcus saccharolyticus*

Except for its presence in this incredibly long list of infectious organisms to be "treated

with an efflux pump inhibitor," *C. difficile* is nowhere else mentioned in the specification. Nowhere is this organism called out specifically for treatment by a rifamycin or any other particular antibiotic.

Neither does Chamberland focus on rifamycins as therapeutic agents. First, it is efflux pump inhibitors, and not antibiotics, that Chamberland touts as effective antibacterial compounds. Moreover, rifamycins at best are listed as just one of *nine different classes of possible antibacterial agents* and one of *141 possible antibacterial agents* that Chamberland indicates can be used in combination with an efflux pump inhibitor. In particular, at column 16, line 46 to column 17, line 26, Chamberland states:

> Also in particular embodiments various antibacterial agents can be used. These include quinolones, tetracyclines, glycopeptides, aminoglycosides, β-lactams, rifamycins, coumermycins, macrolides, and chloramphenicol. In particular embodiments an antibiotic of the above classes can be, for example, one of the following:
>
> β-Lactam Antibiotics
>
> imipenem, meropenem, biapenem, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefixime, cefinenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, cefpimizole, cefpiramide, cefpodoxime, cefsulodin, ceftazidime, cefteram, ceftezole, ceftibuten, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephaacetrile, cephalexin, cephaloglycin, cephaloridine, cephalothin, cephapirin, cephradine, cefinetazole, cefoxitin, cefotetan, azthreonam, carumonam, flomoxef, moxalactam, amidinocillin, amoxicillin, ampicillin, azlocillin, carbenicillin, benzylpenicillin, carfecillin, cloxacillin, dicloxacillin, methicillin, mezlocillin, nafcillin, oxacillin, penicillin G, piperacillin, sulbenicillin, temocillin, ticarcillin, cefditoren, SC004, KY-020, cefdinir, ceftibuten, FK-312, S-1090, CP-0467, BK-218, FK-037, DQ-2556, FK-518, cefozopran, ME1228, KP-736, CP-6232, Ro 09-1227, OPC-20000, LY206763
>
> Macrolides
>
> azithromycin, clarithromycin, erythromycin, oleandomycin, rokitamycin, rosaramicin, roxithromycin, troleandomycin

Quinolones

amifloxacin, cinoxacin, ciprofloxacin, enoxacin, fleroxacin, flumequine, lomefloxacin, nalidixic acid, norfloxacin, ofloxacin, levofloxacin, oxolinic acid, pefloxacin, rosoxacin, temafloxacin, tosufloxacin, sparfloxacin, clinafloxacin, PD131628, PD138312, PD140248, Q-35, AM-1 155, NM394, T-3761, rufloxacin, OPC-17116, DU-6859a (identified in Sato, K. et al., 1992, Antimicrob Agents Chemother. 37:1491-98), DV-7751a (identified in Tanaka, M. et al., 1992, Antimicrob. Agents Chemother. 37:2212-18)

Tetracyclines

chlortetracycline, demeclocycline, doxycycline, lymecycline, methacycline, minocycline, oxytetracycline, tetracycline

Aminoglycosides

amikacin, arbekacin, butirosin, dibekacin, fortimicins, gentamicin, kanamycin, meomycin, netilmicin, ribostamycin, sisomicin, spectinomycin, streptomycin, tobramycin, clindamycin, lincomycin.

Indeed, this list includes most, if not all, major antibiotics known to medical practitioners.

Inclusion of *C. difficile* and rifamycins in two such all-inclusive lists cannot form the basis for the assertion that Chamberland *specifically* teaches that "rifamycins can be used to treat *Clostridium Difficile,*" as suggested by the Office. Neither can the alternative support provided by the Office -- claims 15, 16, and 25 – support this rejection. These claims do not describe the treatment of a *C. difficile* infection using a rifamycin. Claim 15 recites the same 89 possible bacteria that can be treated using the methods of co-administration of an efflux pump inhibitor and any antimicrobial agent. Claim 16 recites the use of any antibacterial agent as the antimicrobial agent, and claim 25 recites the use of a rifamycin as a possible antibacterial agent. These claim citations are no more particular in their teachings than the specification as a whole. For example, claim 15 again lists all possible organisms for treatment, and claims 17 to 25 encompass

all nine of the possible classes of antibacterial agents that are provided in the specification.[1] These claims, like the remainder of Chamberland, do not specifically refer to the treatment of the particular bacterium, *C. difficile*, with the specific antibiotic class, rifamycins. Given Chamberland's lack of suggestion or guidance, the skilled artisan reading this reference would not be led to the selection of a rifamycin to treat *C. difficile*. Reliance on this basis for the rejection should be withdrawn.

Turning to the secondary reference, Rose, this reference describes a method for the treatment of a bacterial infection using a once-weekly or twice-weekly administration of rifalazil. Even if Applicant stipulates that Rose "teaches that rifalazil is a known rifamycin that is known to treat bacterial infections," as suggested by the Office, this does not remedy the deficiencies of Chamberland. As indicated above, Chamberland does not provide the specific teaching that rifamycins should be used to treat infections of *C. difficile*. Accordingly, these references even in combination do not support a *prima facie* case of obviousness. The § 103 rejection of claims 1-11 and 54-58 should be withdrawn.

Rejection of Claims 13, 34, 35, 37-53, 59, 73-75 under 35 U.S.C. § 103(a)

Claims 13, 34, 35, 37-53, 59, and 73-75 also stand rejected for obviousness over Chamberland in view of Rose and in further combination with Bostwick. Applicant respectfully traverses this rejection.

Claims 13, 34, 35, 37-53, 59 and 73-75 feature methods and compositions for

[1] The Office cannot focus on claim 25 in isolation, but must consider the claim in the context of the other claims

treating a subject having a *C. difficile* infection by administering to the subject an effective amount of rifalazil in combination with one or more particular antibiotics.

For this rejection, the Office states that the teachings of Chamberland and Rose, as described for the previous § 103 rejection, render the present claims obvious when further combined with Bostwick's teaching that vancomycin and metronidazole are known to treat *C. difficile* in combination with other active agents. This rejection is traversed because Bostwick does not cure the deficiencies of Chamberland described above and actually teaches away from the present invention.

Specifically, Bostwick teaches the use of an antibody having activity against *C. difficile* and its use for treating a human suffering from a *C. difficile* infection. Bostwick states that the use of an antibody therapeutic is particularly effective in the treatment of *C. difficile* because it does not disrupt the colonic flora, one of the known limitations of current antibiotic therapies. Bostwick also describes the combination of their antibody therapy with the known antibiotics vancomycin, bacitracin, and metronidazole.

Applicant agrees that vancomycin and metronidazole were known to ameliorate *C. difficile* infections at the time the invention was made. However, these treatments were also known to be ineffective in up to 20% of cases, thereby presenting a need for improved methods for treating *C. difficile* infections. Bostwick's improvement features the use of an antibody (a non-antibacterial agent) having specific activity against *C. difficile*. Applicant's improvement features the use of rifalazil, an antibiotic *that was not*

17-25, as is required for any prior art teaching.

previously known to be effective for the treatment of *C. difficile* infections.

As discussed in detail above, the primary reference, Chamberland, does not teach that rifamycins can be used to treat *C. difficile* infections, nor does Chamberland provide any suggestion or direction guiding the skilled artisan towards the selection of a rifamycin for the treatment of an infection of *C. difficile*. Rose does not remedy this deficiency. Bostwick also does not remedy this deficiency because Bostwick makes no mention of rifalazil for the treatment of a *C. difficile* infection. Rather, Bostwick requires the use of antibodies specific for *C. difficile* and provides advantages for the use of antibodies over antibacterial agents, which can affect the colonic flora and also result in relapse of symptoms. Bostwick therefore also teaches away from the present invention because a skilled artisan after reading Bostwick would not be motivated to combine *two* antibiotics (much less specifically combine rifalazil with a second antibiotic), as Bostwick teaches that antibiotics are less effective and should be replaced by antibodies.

The combination of Chamberland, Rose, and Bostwick therefore cannot be used as the basis for a *prima facie* case of obviousness for any of claims 13, 34, 35, 37-53, 59, or 73-75. This rejection should also be withdrawn.

Rejection of Claims 12, 14-33, 36, and 60-72 under 35 U.S.C. § 103(a)

Claims 12, 14-33, 36, and 60-72 stand further rejected for obviousness over Chamberland in view of Rose and in further combination with the admission of Applicant in his specification. Applicant respectfully traverses this rejection.

For this rejection, the Office combines the arguments relied on for the previous obviousness rejections with the additional assertion that, although Chamberland does not list all of the recited antibiotics as being known, Applicant admits in his own specification that the recited drugs are known and have known dosages.

The invention covered by claims 12, 14-33, 36, and 60-72 features the use of an effective amount of rifalazil in combination with one or more additional agents, including second antibiotics, for treating a subject having an infection of *C. difficile*. The presence of a statement in Applicant's specification that the additional drugs that are to be used in combination with rifalazil in the methods and compositions of the present invention are known and have known dosages does not render the present invention obvious. It is the combination of such known drugs with *rifalazil* that is claimed in claims 12, 14-33, 36, and 60-72. This combination was not known at the time the invention was made because rifalazil was not taught or suggested by Chamberland or Rose (or elsewhere in the prior art) for use in treating *C. difficile*. The fact that other antibiotics were known and their dosages determined is of no significance to the patentability of Applicant's basic invention – the use of rifalazil to treat *C. difficile*. The § 103 rejection of claims 12, 14-33, 36, and 60-72 should be withdrawn.

CONCLUSION

Applicant submits that the claims are now in condition for allowance and such action is respectfully requested.

Enclosed is a petition to extend the period for replying two months, to and including October 19, 2004.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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